Exploratory Research and Hypothesis in Medicine **2026** vol. 11(2) | e00079
DOI: 10.14218/ERHM.2025.00079

Mini Review

Perioperative Anaphylaxis: Etiology, Pathophysiology, Diagnostic Challenges, Immediate Management, Prevention Strategies, and Future Perspectives

Huiqiao Lian[1,2#], Weihan Fu[3#], Xuli Ren[3,4*] and Fang Wang[4]

[1]*Department of Anesthesiology, The First Hospital of Jilin University, Changchun, Jilin, China;* [2]*Changchun Jirun Jingyue Hospital, Changchun, Jilin, China;* [3]*Department of Anesthesiology, The Third Hospital of Jilin University, Changchun, Jilin, China;* [4]*School of Basic Medicine, Jilin Medical University, Changchun, Jilin, China*

Received: December 04, 2025 | **Revised:** February 03, 2026 | **Accepted:** February 28, 2026 | **Published online:** March 17, 2026

Abstract

Perioperative anaphylaxis is a rare, life-threatening, iatrogenic condition that predominantly arises following anesthesia. The unique context of this condition, characterized by the concurrent administration of multiple drugs, patient draping, and altered physiological states, presents significant diagnostic and therapeutic challenges, contributing to a higher mortality rate compared to anaphylaxis in other settings. This narrative review synthesizes the evidence to delineate the evolving etiology, pathophysiology, atypical clinical presentation, evidence-based immediate management, and strategic prevention of perioperative anaphylactic reactions. The primary causative agents include neuromuscular blocking agents, antibiotics, and latex, with emerging culprits such as chlorhexidine, dyes, and novel agents like remimazolam. Diagnosis is complicated by the paucity of cutaneous signs; thus, cardiovascular collapse combined with a low end-tidal carbon dioxide level has emerged as a useful supportive diagnostic indicator that requires integration with the clinical context. Immediate management prioritizes the prompt administration of epinephrine and aggressive fluid resuscitation. Subsequent allergological investigations, primarily via skin testing and serum tryptase/histamine measurement, are paramount for identifying the causative agent and preventing its recurrence. Prevention strategies emphasize meticulous history-taking, risk stratification, and the creation of latex-free environments. Future directions must focus on establishing global surveillance networks, exploring novel biomarkers and risk factors such as the circulating microbiome—a preliminary but promising area of research—and enhancing team preparedness through simulation training to improve patient safety outcomes.

Introduction

Perioperative anaphylaxis is a rare but potentially life-threatening condition that occurs during anesthesia, with an estimated incidence between 1:2,000 and 1:20,000 procedures.[1,2] However, its rapid progression and severe clinical consequences mean it carries a higher mortality rate compared to other forms of anaphylaxis. The diagnosis of perioperative anaphylaxis is particularly challenging due to the physiological changes associated with anesthesia, such as the absence of subjective symptoms and the simultaneous use of multiple potential triggers, which often obscure the classic clinical signs.[3]

While several studies have contributed to our understanding of this rare phenomenon, the majority of existing evidence remains heterogeneous and is often based on small case series or anecdotal reports. Furthermore, many clinicians struggle to integrate evolving knowledge into real-time perioperative decision-making.[4] We conducted a search of PubMed using the predefined keywords "perioperative anaphylaxis," covering studies published from 2017 to 2025. As listed in Table 1, this review synthesizes recent findings regarding the pathophysiology, the evolving etiology, atypical clinical presentation, evidence-based immediate management, and strategic prevention of perioperative anaphylactic reactions, with a focus on improving clinical decision-making and patient safety.

Keywords: Perioperative anaphylaxis; Etiology; Pathophysiology; Dagnosis; Management; Prevention strategies.

***Correspondence to:** Xuli Ren, Department of Anesthesiology, The Third Hospital of Jilin University, 126 Xiantai Street, Erdao District, Changchun, Jilin 130033, China. ORCID: https://orcid.org/0009-0007-2857-163X. Tel: +86-15584028805, E-mail: xlren22@jlu.edu.cn

[#]These authors contributed equally to this work.

How to cite this article: Lian H, Fu W, Ren X, Wang F. Perioperative Anaphylaxis: Etiology, Pathophysiology, Diagnostic Challenges, Immediate Management, Prevention Strategies, and Future Perspectives. *Explor Res Hypothesis Med* 2026;11(2):e00079. doi: 10.14218/ERHM.2025.00079.

Table 1. Perioperative anaphylaxis: triggers, diagnostic clues, management, and evidence level

Category	Key points	Clinical notes	Level of evidence
Common triggers	Neuromuscular blocking agents (e.g., rocuronium, succinylcholine)	Most frequently implicated agents; reactions may occur on first exposure due to cross-reactivity	Large observational studies, registry data, guidelines
	Antibiotics (especially β-lactams)	Often administered during induction; timing may aid identification	Cohort studies, systematic reviews
	Latex	Incidence reduced in latex-free environments; still relevant in high-risk populations	Epidemiologic studies, guidelines
Emerging triggers	Chlorhexidine	Increasingly recognized; often overlooked without targeted testing	Case series, observational studies
	Dyes (e.g., patent blue)	Typically associated with specific surgical procedures	Case series
	Remimazolam	Reported in isolated cases; incidence and cross-reactivity remain unclear	Case reports only
Key diagnostic clues	Severe hypotension	Most common presenting feature; nonspecific	Observational studies
	Bronchospasm	Often severe and associated with cardiovascular instability	Observational studies
	Low end-tidal CO_2 ($ETCO_2$)	Highly suggestive when occurring with hypotension shortly after induction; not specific	Case–control study
Biomarkers	Serum tryptase	Supports mast cell activation; normal levels do not exclude anaphylaxis	Prospective studies
	Plasma histamine	Early but short-lived marker; timing of sampling is critical	Prospective studies
Immediate management	Epinephrine administration	First-line therapy; dose and route depend on severity	International guidelines
	Fluid resuscitation	Large volumes often required due to capillary leak	Guidelines, clinical consensus
Post-event investigation	Skin testing	Cornerstone for identifying culprit agents; timing may vary	Practice guidelines
	Specific IgE testing	Supplementary role for selected agents (e.g., latex, some NMBAs)	Observational studies
Prevention strategies	Preoperative risk assessment	Focus on prior reactions, atopy, and known exposures	Guidelines
	Allergen avoidance (e.g., latex-free environment)	Most effective preventive measure in high-risk patients	Epidemiologic evidence
Future directions	Circulating microbiome	Exploratory, hypothesis-generating; no current clinical application	Pilot study
	Simulation-based training	Improves recognition and crisis management performance	Simulation studies

IgE, immunoglobulin E; NMBAs, neuromuscular blocking agents.

Pathophysiological mechanisms and the evolving etiological landscape

Perioperative anaphylaxis is predominantly an immediate hypersensitivity reaction, typically mediated by allergen-specific immunoglobulin E (IgE), which induces mast cell and basophil degranulation. Non-IgE-mediated (anaphylactoid) reactions, characterized by direct mediator release, also occur and complicate the pathophysiological understanding.[5] These mediators contribute to vasodilation, increased vascular permeability, and bronchoconstriction, culminating in cardiovascular collapse and respiratory distress.[6]

Primary and evolving triggers

Extensive research over several decades consistently identifies neuromuscular blocking agents (NMBAs) as the predominant cause of perioperative anaphylaxis.[7,8] Documented reactions have occurred with various NMBAs, ranging from pancuronium to rocuronium.[9] Antibiotics, particularly beta-lactams used for surgical prophylaxis, represent the second most prevalent cause of perioperative anaphylaxis.[2] Latex allergy was previously a significant cause[10]; however, its incidence has declined in environments implementing effective latex-avoidance policies.[1] The etiological landscape of this condition is continually evolving. Chlorhexidine, a widely utilized antiseptic, and dyes such as patent blue are increasingly recognized as significant triggers.[1] Notably, remimazolam has been increasingly reported as a potential trigger of perioperative anaphylaxis in recent case reports and small case series.[11–14] Some reports have suggested possible cross-reactivity with midazolam[13]; however, these observations remain inconclusive and are based on isolated cases, underscoring the need for larger pharmacovigilance datasets and further mechanistic investigations.

High-risk populations

There are identifiable risk factors associated with latex allergy. High-risk groups include individuals with a genetic predisposition, those with increased prior exposure, such as patients with spina bifida or those requiring chronic bladder catheterization, healthcare workers exposed via inhalation, and patients who have undergone multiple surgeries.[15] These considerations emphasize the importance of a meticulous preoperative history.

Exploration of emerging and experimental risk factors

Recent research has initiated an exploration of host-intrinsic factors that extend beyond direct allergen exposure. A key study examined bacterial DNA signatures in blood of patients with NMBA-related allergic reactions.[16] It found differences in the types and amounts of certain bacteria, like Enterobacteriaceae and Veillonellaceae, compared to healthy people. These bacteria were linked to tryptase and specific IgE levels. These findings may help explain why some people are more susceptible to drug allergies and may provide insights into the mechanisms underlying these reactions.[17] Although promising, these findings are based on a limited sample size and should be considered exploratory at this stage. Further validation in larger cohorts is essential before any clinical recommendations can be made.

Clinical diagnostic challenges and advances

Atypical clinical presentation

Diagnosing anaphylaxis during anesthesia presents a unique challenge due to its atypical clinical presentation. The lack of spontaneous breathing and the extensive use of sterile draping often hinder direct observation of skin color and other cutaneous changes. Unlike community-onset anaphylaxis, manifestations such as erythema or urticaria are significantly less common during intraoperative events.[1] Instead, the initial clinical indicator is often cardiovascular collapse, most commonly manifesting as severe hypotension.[18] This hemodynamic instability can easily be mistaken for the pharmacological effects of anesthetic agents, and when combined with the patient's draped position and the simultaneous administration of multiple drugs, it significantly complicates timely recognition and accurate clinical assessment.[3]

Key diagnostic indicators

When diagnosing severe low blood pressure during surgery, it is important to check for anaphylaxis, a serious allergic reaction. Low blood pressure is common but not specific to anaphylaxis.

End-tidal carbon dioxide ($ETCO_2$) monitoring is a valuable diagnostic tool.[18] A key study found that in patients with severe low blood pressure after anesthesia, a low $ETCO_2$ value is a strong sign of anaphylaxis. The study showed that the average lowest $ETCO_2$ was much lower in the anaphylaxis group than in those with low blood pressure from other causes (17 mmHg vs. 32 mmHg; $P < 0.001$). The accuracy of this test was very high, with an area under the curve of 0.95 (95% confidence interval: 0.91–0.99). For a cutoff value of about 23 mmHg, the test was 92% sensitive and 94% specific for anaphylaxis. This indicates a serious mismatch in ventilation and blood flow due to bronchospasm and increased dead-space ventilation.

However, low $ETCO_2$ is not specific to anaphylaxis and can also be observed in other causes of circulatory collapse (e.g., massive hemorrhage, pulmonary embolism). Accordingly, $ETCO_2$ should be interpreted as a supportive bedside marker within the broader clinical and hemodynamic context, not as a standalone diagnostic criterion.

Bronchospasm is another key indicator of anaphylaxis and can manifest either independently or alongside other symptoms.[19,20] In cases of perioperative anaphylaxis (Ring and Messmer grades III–IV), bronchospasm often forms part of a severe clinical presentation. Anaphylactic bronchospasm is typically more intense and is frequently accompanied by other anaphylactic signs, such as hypotension, cutaneous flushing, and angioedema, which aid in its identification. In patients with tracheal intubation, there is a notable increase in airway pressure.

The role of biomarkers

Serum tryptase

The measurement of serum tryptase levels is essential for confirming mast cell activation in cases of perioperative hypersensitivity. In a prospective, observational study, elevated serum tryptase levels were observed in 71.4% of patients with suspected hypersensitivity reactions, serving as a significant indicator for distinguishing immune-mediated responses.[21]

Plasma histamine

This mediator rises earlier but has a very short half-life. Obtaining blood samples both immediately and within 1–2 h of onset improves diagnostic yield; reported thresholds (e.g., ~1.5 ng/mL at ~30 min) offer high specificity but should be interpreted alongside clinical findings.[21]

Immediate management and subsequent investigation

Acute resuscitation

Early epinephrine administration has been shown to significantly im-

prove survival outcomes.[1] The protocol includes stopping the infusion of potential triggers, calling for help, administering 100% oxygen, initiating aggressive fluid resuscitation with crystalloids, and administering intramuscular or intravenous epinephrine titrated to the response. These steps are concordant with recent practical guidance and authoritative clinical reviews, underscoring epinephrine as first-line therapy and the frequent need for large-volume fluids due to capillary leak.[22]

Post-stabilization allergological workup

Once the patient is stabilized, it is imperative to conduct a systematic investigation to identify the causative agent.

Skin testing

Skin prick and intradermal tests are the cornerstone of diagnosis for most anesthetic drugs.[23] Fisher's early work established the value of these tests for reactions to induction agents and NMBAs.[24] They are traditionally performed four to six weeks post-reaction. When expedited surgery is required, carefully selected early testing may be considered in specialized settings.

Drug provocation tests

Drug provocation tests can be considered in cases of high clinical suspicion with negative skin tests. In cases of high clinical suspicion with negative skin test results, a carefully graded drug challenge may be considered in a highly controlled setting. A case report used a provocation test to definitively diagnose remimazolam allergy, highlighting its definitive role while acknowledging its inherent risks.[13] This approach can be definitive but carries inherent risks and is reserved for expert centers.

In vitro testing

Specific IgE assays (for latex, certain NMBAs, and antibiotics) can provide supplementary evidence.[15]

Prevention strategies and future directions

A Prevention-centric paradigm

Preoperative assessment

Meticulous history focusing on previous allergic reactions, atopy, and specific exposures (e.g., latex) is essential.

Risk stratification and labelling

Screening high-risk patients (e.g., those with latex allergy) and clear labelling of medical records.

Allergen-safe environments

The establishment of latex-free zones, particularly in operating and recovery rooms, is a critical preventive measure. Avoiding known trigger drugs is also important.

Premedication

Pretreatment regimens with antihistamines and corticosteroids, effective for preventing some radiocontrast media reactions, are not effective in preventing latex-induced anaphylaxis. Therefore, environmental control and avoidance are central.

Future research and unmet needs

Epidemiological surveillance

The likely causative agent varies by geographic location. Globally, antibiotics (specifically penicillins and cephalosporins) are most frequently connected with fatal drug anaphylaxis.[25] Establishing international, standardized registries (modelled on projects such as NAP 6) is vital to track the evolving etiology and incidence in real time.[2]

Diagnostic optimization

There are no prospective randomized studies that have evaluated the use of a specific protocol of premedication for the prevention of perioperative anaphylaxis.16 Therefore, it is critical to identify and evaluate at-risk patients before any surgical procedure.[26]

Mechanistic studies and risk prediction

The findings on the circulating microbiome are preliminary but potentially important. Larger studies are required to validate whether microbial signatures can serve as predictive or diagnostic biomarkers and to elucidate their mechanistic links to immune dysregulation.[16] Microbiome-associated signatures need validation, and mechanistic links to immune dysregulation should be clarified.

Safety evaluation of novel agents

Expand pharmacovigilance for remimazolam and other emerging agents to define incidence and cross-reactivity.

Simulation and team training

A study used eye-tracking to analyze anesthesiologists' visual attention during simulated crises and found that experienced providers allocated attention more effectively.[26] High-fidelity simulation improves recognition and crisis management; ongoing team training should be embedded into perioperative safety programs.

Limitations

This is a narrative (not systematic) review. Although we used a structured search of PubMed and screened reference lists, publication bias and incomplete retrieval remain possible. Evidence for several topics (e.g., remimazolam, chlorhexidine) derives largely from case reports or small series, limiting generalizability and precluding incidence estimates. The microbiome literature is preliminary and hypothesis-generating. Recommendations are aligned with contemporary guidance but may require local adaptation.

Conclusions

Perioperative anaphylaxis poses a dynamic and formidable challenge in the field of anesthesiology. Its pathophysiology is complex, its presentation is often masked by the state of anesthesia, and its diagnosis requires a high index of suspicion, guided by specific signs such as profound hypotension coupled with low $ETCO_2$. The acute management of anaphylaxis must be swift and protocol-driven, focusing on epinephrine and volume expansion. Long-term patient safety relies on systematic prevention, including risk-aware preoperative evaluation, awareness of both traditional and emerging triggers (latex, chlorhexidine, and remimazolam), and implementation of allergen avoidance protocols. By integrating updated guidance, critically appraising the evidence base for emerging agents, and summarizing practical diagnostic and management steps, this review aims to support timely recognition and effective treatment. Future priorities include international surveillance, biomarker development, rigorous evaluation of novel agents, and sustained team training

Acknowledgments

None.

Funding

None.

Conflict of interest

The authors have no other conflicts of interest to note.

Author contributions

Study conception and design (XR), data acquisition, data analysis, data interpretation, drafting of the manuscript (HL), critical revision of the manuscript for significant intellectual content (WF), administrative, technical, or material support, and study supervision (FW). All authors have made substantial contributions to this study and have approved the final manuscript.

References

[1] Hsu Blatman KS, Hepner DL. Current Knowledge and Management of Hypersensitivity to Perioperative Drugs and Radiocontrast Media. J Allergy Clin Immunol Pract 2017;5(3):587–592. doi:10.1016/j.jaip.2017.03.016, PMID:28483312.

[2] Kosciuczuk U, Knapp P. What do we know about perioperative hypersensitivity reactions and what can we do to improve perioperative safety? Ann Med 2021;53(1):1772–1778. doi:10.1080/07853890.2021.1976818, PMID:34632895.

[3] Lieberman P. Anaphylactic reactions during surgical and medical procedures. J Allergy Clin Immunol 2002;110(2 Suppl):S64–S69. doi:10.1067/mai.2002.124970, PMID:12170245.

[4] Tacquard C, Iba T, Levy JH. Perioperative Anaphylaxis. Anesthesiology 2023;138(1):100–110. doi:10.1097/ALN.0000000000004419, PMID:36413685.

[5] Peroni DG, Sansotta N, Bernardini R, Cardinale F, Paravati F, Franceschini F, *et al*. Perioperative allergy: clinical manifestations. Int J Immunopathol Pharmacol 2011;24(3 Suppl):S69–S74. doi:10.1177/03946320110240s310, PMID:22014928.

[6] Garvey LH, Ebo DG, Mertes P, *et al*. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. Allergy 2019;74(10):1872–1884. doi:10.1111/all.13820, PMID:30964555.

[7] Au EYL, Lau CS, Lam K, Chan E. Perioperative anaphylaxis and investigations: a local study in Hong Kong. Singapore Med J 2020;61(4):200–205. doi:10.11622/smedj.2019156, PMID:31788702.

[8] Norawat R, Vohra A, Parkes A, O'Keeffe NJ, Anipindi S, Maybauer MO. Incidence and outcome of anaphylaxis in cardiac surgical patients. Ann Card Anaesth 2022;25(3):323–329. doi:10.4103/aca.aca_170_21, PMID:35799561.

[9] Neal SM, Manthri PR, Gadiyar V, Wildsmith JA. Histaminoid reactions associated with rocuronium. Br J Anaesth 2000;84(1):108–111. doi:10.1093/oxfordjournals.bja.a013365, PMID:10740560.

[10] Manian DV, Volcheck GW. Perioperative Anaphylaxis: Evaluation and Management. Clin Rev Allergy Immunol 2022;62(3):383–399. doi:10.1007/s12016-021-08874-1, PMID:34247332.

[11] Tsurumi K, Takahashi S, Hiramoto Y, Nagumo K, Takazawa T, Kamiyama Y. Remimazolam anaphylaxis during anesthesia induction. J Anesth 2021;35(4):571–575. doi:10.1007/s00540-021-02934-8, PMID:34050439.

[12] Nakai T, Kako E, Ota H, So M, Sobue K. Remimazolam anaphylaxis in a patient not allergic to brotizolam: a case report and literature review. BMC Anesthesiol 2024;24(1):204. doi:10.1186/s12871-024-02591-w, PMID:38851690.

[13] Lee S, Park J, Kim NH, Hong H, Sohn KH, Kang HY, *et al*. Remimazolam Anaphylaxis during Induction of General Anesthesia Confirmed by Provocation Test-A Case Report and Literature Review. Medicina (Kaunas) 2023;59(11):1915. doi:10.3390/medicina59111915, PMID:38003965.

[14] Kim KM, Lee H, Bang JY, Choi BM, Noh GJ. Anaphylaxis following remimazolam administration during induction of anaesthesia. Br J Anaesth 2022;129(5):e122–e124. doi:10.1016/j.bja.2022.07.047, PMID:36055819.

[15] Swartz J, Braude BM, Gilmour RF, Shandling B, Gold M. Intraoperative anaphylaxis to latex. Can J Anaesth 1990;37(5):589–592. doi:10.1007/BF03006333, PMID:2197008.

[16] de Chaisemartin L, Ciocan D, Gouel-Chéron A, Granger V, Longrois D, Montravers P, *et al*. Circulating microbiome analysis in patients with perioperative anaphylaxis. Front Immunol 2023;14:1241851. doi:10.3389/fimmu.2023.1241851, PMID:38274796.

[17] Ebo DG, Clarke RC, Mertes PM, Platt PR, Sabato V, Sadleir PHM. Molecular mechanisms and pathophysiology of perioperative hypersensitivity and anaphylaxis: a narrative review. Br J Anaesth 2019;123(1):e38–e49. doi:10.1016/j.bja.2019.01.031, PMID:30916022.

[18] Erlich C, Lamer A, Moussa MD, Martin J, Rogeau S, Tavernier B. End-tidal Carbon Dioxide for Diagnosing Anaphylaxis in Patients with Severe Postinduction Hypotension. Anesthesiology 2022;136(3):472–481. doi:10.1097/ALN.0000000000004123, PMID:35041738.

[19] Fisher MM, Ramakrishnan N, Doig G, Rose M, Baldo B. The investigation of bronchospasm during induction of anaesthesia. Acta Anaesthesiol Scand 2009;53(8):1006–1011. doi:10.1111/j.1399-6576.2009.02044.x, PMID:19572931.

[20] Baronos S, Selvaraj BJ, Liang M, Ahmed K, Yarmush J. Sugammadex-induced bronchospasm during desflurane anaesthesia. Br J Anaesth 2019;123(1):e155–e156. doi:10.1016/j.bja.2019.04.001, PMID:31027913.

[21] Horiuchi T, Takazawa T, Haraguchi T, Orihara M, Nagumo K, Saito S. Investigating the optimal diagnostic value of histamine for diagnosing perioperative hypersensitivity: a prospective, observational study. J Anesth 2023;37(4):645–649. doi:10.1007/s00540-023-03199-z, PMID:37156974.

[22] Admass BA, Hassen AE, Agegnehu AF, Temesgen MM, Gebeyehu NA, Ferede YA, *et al*. Management of perioperative anaphylaxis: systematic review. Int J Surg Open 2023;52:100595. doi:10.1016/j.ijso.2023.100595.

[23] Takazawa T, Yamaura K, Hara T, Yorozu T, Mitsuhata H, Morimatsu H, *et al*. Practical guidelines for the response to perioperative anaphylaxis. J Anesth 2021;35(6):778–793. doi:10.1007/s00540-021-03005-8, PMID:34651257.

[24] Dejoux A, de Chaisemartin L, Bruhns P, Longrois D, Gouel-Chéron A. Neuromuscular blocking agent induced hypersensitivity reaction exploration: an update. Eur J Anaesthesiol 2023;40(2):95–104. doi:10.1097/EJA.0000000000001765, PMID:36301083.

[25] Kalangara J, Vanijcharoenkarn K, Lynde GC, McIntosh N, Kuruvilla M. Approach to Perioperative Anaphylaxis in 2020: Updates in Diagnosis and Management. Curr Allergy Asthma Rep 2021;21(1):4. doi:10.1007/s11882-020-00980-y, PMID:33409706.

[26] Capogna E, Salvi F, Delvino L, Di Giacinto A, Velardo M. Novice and Expert Anesthesiologists' Eye-Tracking Metrics During Simulated Epidural Block: A Preliminary, Brief Observational Report. Local Reg Anesth 2020;13:105–109. doi:10.2147/LRA.S267879, PMID:32922069.